VOL. 21, NO. 6 JUNE 1966

Food Drug Cosmetic Law JOURNAL

Question and Answer Panel of the FDA-FLI Ninth Annual Educational Conference

Latin-American Food Code, Chapter VII

A COMMERCE CLEARING HOUSE PUBLICATION
PUBLISHED IN ASSOCIATION WITH THE FOOD AND DRUG LAW INSTITUTE, INC.

THE EDITORIAL POLICY of this JOURNAL is to record the progress of the law in the field of food, drugs and cosmetics, and to provide a constructive discussion of it, according to the highest professional standards. The FOOD DRUG COSMETIC LAW JOURNAL is the only forum for current discussion of such law and it renders an important public service, for it is an invaluable means (1) to create a better knowledge and understanding of food, drug and cosmetic law, (2) to promote its due operation and development and thus (3) to effectuate its great remedial purposes. In short: While this law receives normal legal, administrative and judicial consideration, there remains a basic need for its appropriate study as a fundamental law of the land; the JOURNAL is designed to satisfy that need. The editorial policy also is to allow frank discussion of food-drug-cosmetic issues. The views stated are those of the contributors and not necessarily those of the publishers. On this basis, contributions and comments are invited.

The FOOD DRUG COSMETIC LAW JOURNAL is published monthly by Commerce Clearing House, Inc. Subscription price: 1 year, $20; single copies, $2. Editorial and business offices, 4025 W. Peterson Ave., Chicago, Ill. 60646. Printed in United States of America.

June, 1966
Volume 21 • Number 6

Second-class postage paid at Chicago, Illinois and at additional mailing offices.

FOOD DRUG COSMETIC LAW JOURNAL

Table of Contents . . . . . June, 1966

VOLUME 21 NUMBER 6

Printed in the United States of America

FOOD DRUG COSMETIC LAW JOURNAL

Editorial Advisory Board

Editor of Comments: Franklin M. Depew

Editor of Canadian Law: Robert E. Curran, Q. C.

Editor of Foreign Law: Julius G. Zimmerman

Associate Editor for Europe: Ernst Abramson, M. D.

Scientific Editor: Bernard L. Oser

REPORTS

TO THE READER

Latin-American Food Code.—Beginning on page 312, Chapter VII of the Latin-American Food Code is reproduced. This chapter concerns edible oils and fats. The translation is by *Ann M. Wolf* of New York. Chapters I-V, XII, XIII, and XVII of the Code appeared in previous issues of this JOURNAL.

Question and Answer Panel of the FDA-FLI Ninth Annual Educational Conference.—In the afternoon session of the 1965 FDA-FLI Conference there was a Question and Answer Panel. The moderator was *Franklin M. Depew*, President of the Food and Drug Law Institute. Answers by eight of the panelists, who were representatives of the FDA, are found in this issue, beginning on page 322. The panelists are: *William W. Goodrich*, Assistant General Counsel for Food and Drugs; *Malcolm R. Stevens*, Assistant Commissioner for Regulations; *Allen E. Rayfield*, Director, Bureau of Regulatory Compliance; *Dr. Frances O. Kelsey*, Chief of the Investigational Drug Branch, Division of New Drugs; *Dr. William H. Summerson*, Director, Bureau of Scientific Research; *Dr. O. L. Kline*, Assistant Commissioner for Science Resources; *Robert S. Roe*, Director, Bureau of Scientific Standards and Evaluation; and *J. Kenneth Kirk*, Assistant Commissioner for Administration.

Toxicologic Aspects of Drug Safety.—This is the topic of a paper by *Dr. Frederick Coulston*, who is with Albany Medical College. The article begins on page 336. The author discusses the past, present and future of toxicology. Modern toxicology began about ten years ago. The FDA played an important role in its beginnings. A major aim of modern toxicology is to determine the basis for logical predictions of toxicity in man. Such predictions depend upon proper choices of the correct animal species for experimentation. Man comes into contact with chemical agents in three main ways: he receives prescription drugs on the authority of his physician; he receives over-the-counter drugs; and he encounters chemical additives in his food. Toxicology must be concerned with toxicologic effects which are symptomatic and usually reversible, and with effects which are chronic and cumulative. There are drugs whose action blocks basic metabolic processes. Dr. Coulston indicates there is a need to know more about the effects of various chemicals on fertility, size and weight of off-spring, fetal mortality, teratogenicity and the growth and development of the new-born and the juvenile.

Clinical Evaluation of Drug Safety.—In this article, beginning on page 348, *Dr. John Litchfield*, who is with Lederle Laboratories, traces the development of new drugs, from laboratory animal studies through trials in man. He mentions the problems entailed by the use of computers to organize data. At this time, computers are not programmed to deal with synonymous terms. There is a communication problem between the clinician and the programmer. Dr. Litchfield considers the matter of risks in laboratory trials and in new drugs which are marketed, concluding that drugs have a high probability of benefit, and a low probability of harm.

VOL. 21, NO. 6 JUNE, 1966

Food·Drug·Cosmetic Law
Journal

Latin-American Food Code 1964 Edition

In August, 1964, the Latin-American Food Code Council Published the Second Edition of the Latin-American Food Code. Information Concerning the Code and the Table of Contents of the New Edition Appeared in the April 1965 Issue of the *Food Drug Cosmetic Law Journal* (Vol. 20, page 238). The First Five Chapters Were Published in the September 1965 Issue; Chapters XII and XIII in the October 1965 Issue; Chapter XVII in the November 1965 Issue and Chapter X in the December 1965 Issue. Chapter VII Appears Below. The Translation Is by Ann M. Wolf of New York City.

Chapter VII: EDIBLE OILS AND FATS

Edible Oils

Article 157—The term "Edible Oils" means any oils named in this Code as fit for human consumption and such other oils as the health authorities may approve in the future.

Edible oils shall be extracted from oleaginous seeds and fruits by processes which meet the hygienic requirements fixed in this Code. They shall at 25° C. be clear in appearance and agreeable in taste and odor, and may not contain any elements other than those which are typical of the oil and conform with the composition of the seeds or fruits from which they have been extracted.

Article 158—Edible oils shall be classified into the following types:

1. Virgin Oil: Oil from any source obtained exclusively by mechanical pressing, which may have been followed by washing, filtration and sedimentation.

2. Refined Oil: Oil from any source that has undergone a purification process in which none but the following operations are permitted: degumming, neutralization, physical decoloration, physical deodori-

zation and cold filtration or winterization. Recovered oils (from soap stock or neutralization paste) or oils distilled from fatty acids, tallows, etc. shall be considered unfit for human consumption.

3. Genuine . . . . . Oil (insert name of plant): Oil obtained from a single vegetable species. When such oil is bottled at factories at which edible oils are prepared from various kinds of seeds, the first batches may contain another oil in a proportion not exceeding 5 percent.

4. Blended cooking oil: Oil which consists of a blend of two or several genuine oils. Its composition shall be disclosed to the health authority whenever this is required.

5. Flavored oil: Oil which has the aroma and taste of the fruit from which it has been extracted. Edible oils are prohibited from being artificially flavored with olives even if such flavoring is declared in the labeling.

Article 159—Edible oils are prohibited from containing extraneous substances intended to flavor or color them or to modify their physical or chemical properties. They may, however, contain any of the antioxidants and rancidity retarders approved by this Code or the health authorities.

Article 160—Edible oil intended for repacking must be stored in suitable containers kept in perfect hygienic condition at all times. Edible oils are prohibited from being bottled in retail outlets or other places at which sales to the public are made, and may not be sold by itinerant vendors. Establishments at which edible oils are repacked and bottled must comply with the general regulations fixed in this Code and, in addition, have rooms used exclusively for this purpose and approved by the competent authority.

Edible oils may be bottled in rigid plastic bottles which may be used only once and may not be re-filled (one-way containers).

Article 161—The following oils shall be considered unfit for human consumption:

1. Oils from oleaginous seeds whose free acidity, expressed as oleic acid, exceeds 0.5 percent;

2. Oils with a positive rancidity reaction;

3. Oils which contain more than 0.5 percent of sediment, extraneous matters, and residues of substances used in the refining process, and oils whose flavor or aroma is different from the flavor or aroma distinctive of genuine oils or blends of genuine oils;

4. Oils extracted by means of unauthorized solvents, and oils containing a residue of the solvent used in the extraction;

5. Oils which contain mineral oils and other extraneous matters;

6. Esterified or recovered oils;

7. Cooking oils which have been heated for more than ten hours;

8. Artificially colored oils.

Article 162—Any solvents intended for use in the extraction of edible oils and fats must be approved by the health authority. Such solvents may be petroleum by-products or synthetic solvents, such as trichloroethylene, cyclohexane, ethyl alcohol, isopropyl alcohol, and others authorized by the health authority.

Petroleum solvents must come from the redistillation of topping naphthas, never from cracking naphthas. They shall be colorless and clear, shall not leave a deposit, may not contain water or extraneous matter, must have a negative Doctor reaction and in distillation tests, have a boiling point not higher than 92° C.

Article 163—The name "Cottonseed Oil" designates the oil extracted from the seeds of cotton plants (various species of Gossypium). Its physical and chemical properties vary generally between the following limits:

Specific gravity at 25/4° C.	0.912 to 0.921
Refractive Index at 25° C.	1,4705 to 1,4720
Butyrorefractometric deviation	67.2 to 69.5
Iodine value (Wijs)	102 to 117
Cloud point (Modified Bellier)	16° to 19.5° C.
Saponification value	192 to 198
Specific sulphuric acid temperature reaction (Tortelli)	66° to 79°
Unsaponifiable residue	1 percent

Article 164—The names "Rape Oil" and "Turnip Oil" designate the oil extracted from the seeds of various Cruciferae, oleiferous species of the genus Brassica (Brassica napus L., Brassica Campestris L., etc.). Its physical and chemical properties vary in general between the following limits:

Specific gravity at 25/4° C.	0.907 to 0.919
Refractive Index at 25° C.	1.4705 to 1.4725
Butyrorefractometric deviation	67.2 to 70.3
Iodine value (Wijs)	95 to 108
Cloud point (Modified Bellier)	17.5° to 26° C.
Saponification value	170 to 180
Specific sulphuric acid temperature reaction (Tortelli)	53° to 67°
Unsaponifiable residue	1 percent

Article 165—The name "Palm Oil" designates the oil obtained from the fruits of the coyol palm tree (Attalea cohune, Mart.). Its physical and chemical properties vary in general between the following limits:

Specific gravity at 15/4° C.	0.868 to 0.871
Refractive Index at 40° C.	1.449 to 1.450
Iodine number	9 to 14
Saponification index	252 to 260
Solidification point of insoluble fatty acids (Titer)	20 to 21

Article 166—The name "Sunflower Oil" designates the oil extracted from the seeds of the sunflower (Helianthus annus L.) Its physical and chemical properties vary in general between the following limits:

Specific gravity at 25/4° C.	0.913 to 0.919
Refractive Index at 25° C.	1.4720 to 1.4741
Butyrorefractometric deviation	69.5 to 72.8
Iodine value (Wijs)	123 to 137
Cloud point (Modified Bellier)	22° to 27° C.
Saponification value	187 to 192
Specific sulphuric acid temperature reaction (Tortelli)	65° to 82°
Unsaponifiable residue	1 percent

Article 167—The name "Corn Oil" designates the oil extracted from the seeds of corn (Zea mais L.). Its physical and chemical properties vary in general between the following limits:

Specific gravity at 25/4° C.	0.914 to 0.920
Refractive Index at 25° C.	1.4705 to 1.4730
Butyrorefractometric deviation	67.2 to 71.1
Iodine value (Wijs)	107 to 120
Cloud point (Modified Bellier)	16° to 22° C.
Saponification value	188 to 195
Specific sulphuric acid temperature reaction (Tortelli)	65° to 83°
Unsaponifiable residue	2 percent

Article 168—The name "Peanut Oil" designates the oil extracted from the seeds of the peanut plant (Arachis hypogaea L.). Its physical and chemical properties vary in general between the following limits:

Specific gravity at 25/4° C.	0.909 to 0.917
Refractive Index at 25° C.	1.4690 to 1.4700
Butyrorefractometric deviation	64.8 to 66.4
Iodine value (Wijs)	92 to 106
Cloud point (Modified Bellier)	38° to 44° C.
Saponification value	187 to 195
Specific sulphuric acid temperature reaction (Tortelli)	45° to 67°
Unsaponifiable residue	1 percent

Article 169—The name "Olive Oil" designates the oil extracted from the fruit of the olive tree (Olea europaea L.). Its physical and chemical properties vary in general between the following limits:

Specific gravity at 25/4° C.	0.907 to 0.917
Refractive Index at 25° C.	1.4663 to 1.4673
Butyrorefractometric deviation	60.7 to 62.2
Iodine value (Wijs)	78 to 90
Cloud point (Modified Bellier)	12° to 16° C.
Saponification value	187 to 195
Specific sulphuric acid temperature reaction (Tortelli)	42° to 54°
Unsaponifiable residue	1.3 percent

The name "Virgin Oil" may be used only for oil obtained through dripping or the first mechanical expression, which may have been followed by washing, filtration and sedimentation. Virgin oils which have undergone a chemical treatment, neutralization or deodorization shall be named: Grade "A" Refined Olive Oil.

Pressed olive oils shall be classified into three commercial types:

Grade I—Fancy Quality. Oil which at a temperature of 20° C. — 2° C. remains clear after stirring, with an acidity of 1 percent, expressed as oleic acid.

Grade II—High Quality. Oil which at a temperature of 20° C. — 2° C. remains clear after stirring, with an acidity of not more than 2 percent, expressed as oleic acid.

Grade III—Standard Quality. Oil which at a temperature of 20° C. — 2° C. remains clear after stirring, with an acidity of not more than 3 percent, expressed as oleic acid.

The name "Grade B Refined Olive Oil" designates olive oil which extracted from olive dregs by means of solvents has been neutralized, bleached and deodorized. Its physical and chemical properties shall vary within the following limits:

Substances insoluble in petroleum ether	0.05 percent
Unsaponifiable residue	2.5 percent
Refractive Index at 25° C.	1.4680 to 1.4688
Butyrorefractometric deviation	63.2 to 64.5
Iodine value (Wijs)	83 to 95
Cloud point (Modified Bellier)	above 18° C.
Free acidity expressed as oleic acid	not more than 0.5 percent

The use of graphic representations of the olive tree or its fruit, and the use of distinctive names ("designaciones de fantasia") containing the word "olive" or the names of regions known as producing olive oil is permitted only in labels, advertisements and literature directed to olive oil.

Article 170—The name "Grapeseed Oil" designates the oil extracted from the seeds of grapes (Vitis vinifera L.). Its physical and chemical properties vary in general between the following limits:

Specific gravity at 25/4° C.	0.906 to 0.925
Refractive Index at 25° C.	1.4730 to 1.4745
Butyrorefractometric deviation	69.5 to 71.9
Iodine value (Wijs)	130 to 140
Cloud point (Modified Bellier)	11° to 16° C.
Saponification value	185 to 195
Specific sulphuric acid temperature reaction	64° to 74°

Article 171—The names "Sesame Oil" and "Gingili Oil" designate the oil extracted from the seeds of sesame (Sesamum indicum L. and Sesamum orientale L.). Its physical and chemical properties vary in general between the following limits:

Specific gravity at 25/4° C.	0.928 to 0.932
Refractive Index at 25° C.	1.475 to 1.476
Butyrorefractometric deviation	74.3 to 76
Iodine value (Wijs)	113 to 130
Specific sulphuric acid temperature reaction (Tortelli)	62° to 68°
Saponification value	188 to 195

Article 172—The name "Soyabean Oil" applies to the oil extracted from the seeds of soya (Glycine soja, Sieb and Zuco, and Soja Hispida Moench). Its physical and chemical properties vary in general between the following limits:

Specific gravity at 25/4° C.	0.917 to 0.924
Refractive Index at 25° C.	1.4720 to 1.4740
Butyrorefractometric deviation	69.5 to 72.7
Iodine value (Wijs)	125 to 135
Cloud point (Modified Bellier)	19° to 21° C.
Saponification value	188 to 195
Specific sulphuric acid temperature reaction (Tortelli)	82° to 95°
Unsaponifiable residue	1.5 percent

Edible Fats

Article 173—The term "Fats" means glyceride esters which at 20° C. are solid, contrary to oils which at that temperature are liquid. Edible fats are animal fats prepared under hygienic conditions from the unmodified, clean adipose tissue of healthy cattle, sheep, hogs, goats and fowl, slaughtered for consumption under the control of health inspectors; or vegetable fats which meet the requirements of this Code, or mixtures of the two. The solidification point of the insoluble fatty acids (Titer Test) of an

edible fat from no matter what source may not be higher than 46° C. Fats whose solidification point is higher may be used at food processing plants only in combination with other fats whose solidification point is lower. Any fats intended for use in the human diet must be clean and free of rancidity, and their acidity, expressed as oleic acid, may not be higher than 1 percent. The amount of extraneous substances normally incorporated during the melting process may not exceed 1 percent, the term "extraneous substances" meaning water, ash and insoluble impurities. The addition of antioxidants and rancidity retarders authorized under this Code or by the Health Authority shall be permitted, and glycerol monostearate or distearate, or mixtures of the two, may be added to fats intended for bread and cake making to improve their emulsifying and plastic qualities. For standards for glycerol monostearate, see Article 583.

Article 174—"Lard" is obtained by melting the adipose tissue of hogs and then submitting the resultant product to a filtration process. It must at 45° C. have a refractive index of between 1.4559 and 1.4609; a butyrorefractometric deviation of between 49 and 52; an iodine value of between 50 and 70; a specific sulphuric acid temperature reaction (Tortelli) at between 38° and 42°; a saponification value of between 192 and 210; a cloud point of between 23° and 38° C. To the labeling of edible lard intended for export the name "pork fat" may be added in parenthesis after the term "lard." The name "Lard oil" means the oil obtained by the separation of most of the oleostearine normally present in lard. It must have an iodine number of between 67 and 83 and a freezing point of between + 1 and −5°. The name "Leaf lard" designates the fat above the kidneys of hogs which in its unpurified stage may be sold only for industrial uses.

Article 175—The term "Tallow," combined with the name of the animal from which it comes (beef or mutton, or a mixture of the two) and the indication of its quality, means the fatty matter extracted by melting the rough tallow or suet fat from which the naturally present oleostearine or olemargarine has not been separated. The melting can be carried out by the usual process in an open pot with a double bottom heated by steam at a temperature of less than 80° C., or by another technological process, at different temperatures and pressures which permit a more exhaustive extraction of the fat from the tissue. Tallow must be a solid, yellowish mass, pleasant in odor and granular in appearance because of the olein trapped in the solid stearin.

The terms "Olemargarine," "Oleopalmitine" "Tripalmitine," and "Oleo oil" mean tallow pressed long enough to extract the largest possible amount of the oleostearine naturally present in it. The melting point of this tallow must lie below 35° C.

The term "Oleo-masa" means whipped and moulded oleomargarine.

The oleostearine extracted during oleomargarine production may be used in the preparation of edible fats, margarine, etc. Its solidification point (temperature at which the insoluble fatty acids solidify) shall not be below 49° C.

Article 176—Edible animal fats obtained by the open pot method or another process, which have a taste "sui generis" known as "suet taste" and for this reason cannot be classified as "tallow" shall, depending upon their origin, be named "Edible Beef Fat," "Edible Mutton Fat," "Cooking Fat," "Beef drippings," etc.

Article 177—The name "Margarine" designates any emulsified edible fat which has the semblance of butter and consists of animal and/or vegetable fats or a mixture of both, with or without the addition of hydrogenated oils or fats, whole or skimmed milk, milk by-products, lactic enzymes or vitamins. Margarine shall have a total fat content of not less than 80 percent and a water content of not more than 16 percent, and must remain solid at a temperature of 20° C. Benzoic acid in a proportion of not more than 1,200 p.p.m. or sorbic acid and sorbic acid salts in a proportion of not more than 500 p.p.m. may be added to it as protective agents, as well as the antioxidants provided for in Article 686. It may be flavored with diacetyl and colored with carotene or annatto and such other substances as the competent health authority may authorize.

Margarine Powder intended for use in cooking, baking, and candy making is prepared by pulverizing an aqueous emulsion of different fats in a tower (Spray) to which stabilizers such as caseine or soja protein, rice or corn, whole or skimmed milk, mineral salts, sugar, phosphates and citrates and other permitted products may be added. In this type of margarine the fat content may be less than 50 percent. Margarine powder shall consist of small spheres with a low specific gravity which have the fat on their inside and the protein-glycidic part on the outside. The hydrophilic layer on the outside permits the powder to dissolve quickly.

Margarine prepared from vegetables exclusively may be designated as "vegetable margarine."

Margarine is prohibited from being prepared in rooms in which butter is made.

Article 178—The terms "Hydrogenated Oil," "Hardened Oil," "Hydrogenated Fat" or "Hardened Fat" designate edible oils and fats subjected to hydrogenation in the presence of catalysts. Their total fat content must not be less than 99 percent and the amount of metal catalyst (nickel, etc.) present in them may not exceed 4 p.p.m.

Article 179—The name "(beef, sheep, goat, etc.) Foot Oil" designates the product obtained by boiling the extremities of cattle, sheep or goats which have been given a clean bill of health by the official inspectors, which has then been properly purified.

Article 180—The term "Marrow Fat" means the fatty substance extracted from the large bones of cattle. Its melting point must lie below 27° C.

The term "Beef Suet" designates the fat obtained from the adipose tissue that surrounds the kidneys of cattle.

Article 181—The name "Duck Fat" designates the purified fatty matter obtained from domestic palmipedes of the family Anatidae. Yellow in color, it shall at 45° C. have a refractive index of between 1.4568 and 1.4578; a saponification value of between 185 and 196, and a melting point of between 26° and 27° C.

Article 182—The name "Peanut Butter" designates the product prepared from roasted ground fresh peanuts to which salt has been added in a proportion of between 1 and 3 percent, the addition of other permitted ingredients being optional. Peanut butter may contain water in a proportion of not more than 13 percent; saccharifiable substances, expressed as starch, in a proportion of not more than 8.5 percent, and total ash in a proportion of not more than 6 percent. Its fat content shall not be less than 40 percent.

Average percentage composition: water 1.5; protein 28; fat 46; assimilable carbohydrates (sugar 4) 14; crude fiber 2, and (salt-free) ash 1.

Article 183—The name "Coconut Oil" designates the purified and bleached fatty matter extracted from the meat of the fruit of the coconut palm (Cocos nucifera and Cocos Butyracea). It must melt at between 20° C. and 28°C.; its iodine value must be between 8 and 10.5; the saponification value between 246 and 268, and the refractive index at 45° C. must lie between 1.3144 and 1.4459.

Article 184—The name "Bacon" may be used only for the adipose tissue, or fat, of hogs. Bacon is sold in pieces called "strips," fresh or salted, with or without the rind, smoked or unsmoked. Bacon whose fatty part shows excessive rancidity or viscosity, a filthy epidermis, or larvae shall be confiscated. Average percentage composition: water 25; protein 9; fat 60; carbohydrates 0.8; ash 5.2.

The name "Salt Pork" ("Panceta") may be used only for a product obtained from the muscles and subcutaneous adipose tissue of the hog's belly, from the sternum to the pubes. It is being sold in pieces called "strips," and may be fresh, salted (cured) or smoked. Average percentage composition (Smoked Salt Pork): water 18; protein 9; fat 68; carbohydrates 0.6; ash 4.5.

Article 185—Fats from diseased animals shall be denatured immediately to prevent their use in foods and may be used only for industrial purposes.

Article 186—Edible fats and oils to be sold to the public must come in their original containers, labeled in accordance with the law. They may be repacked and bottled only at the plants at which they are prepared, or in warehouses or annexes belonging to the same, and at specialized wholesale houses which hold a permit from the health authority. **[The End]**

Question and Answer Panel of the FDA—FLI Ninth Annual Educational Conference

The Ninth Annual Educational Conference of The Food Law Institute and the Food and Drug Administration Featured a Question and Answer Panel. The Panel, Composed of Representatives of the FDA, Answered Questions Submitted in Writing. Mr. Franklin M. Depew Was Moderator.

Status of FDA's Litigation

Mr. Depew: What is the status of the Food and Drug Administration's (FDA) litigation with: (1) the Toilet Good's Association (TGA) and what exactly are the issues; (2) Pharmaceutical Manufacturer's Association (PMA), over the records and reports requirements, of the Kefauver-Harris Drug Amendments; and (3) PMA over the "generic name everytime" matter?

Mr. Goodrich: Maybe I should start with the third case, the "generic name everytime." This was a suit by the PMA and 37 members of the drug industry to obtain an injunction and a declaratory judgment that we have no authority to issue a regulation specifying that the generic name appear each time the trade name was used in drug advertising and in labeling. We moved to dismiss on the grounds that the case was not ready for presentation but involved a hypothetical issue. Unfortunately, we were defeated in Wilmington, and, fortunately, they were defeated in Philadelphia. The Supreme Court has granted certiorari. We should have a decision in that case from the Supreme Court on whether regulations are reviewable in a suit for declaratory judgment some time next fall.

This case was followed in New York by the TGA case where the Toilet Goods Association and a number of its members sued for a declaratory judgment, that our color additive regulations were illegal. The issues there are, first, that the TGA contends that the term "color additives" doesn't include lipstick, rouge, and other color cosmetics; that the law is intended to apply only to the color

component of these cosmetics; and that we illegally interpreted the statutory definition to cover the color cosmetics. Second, they contend that the interpretation that we put on diluents which are allowed to be used with color additives is too broad. Third, they contend that our regulations on inspection authority are illegal, and that finally, the restriction we put on the exemption for hair dyes containing poisonous and deleterious substances was unwarranted. We stated that the hair dye exception, which exempts hair dyes which caused allergic reactions from the ban against poisonous and deleterious ingredients, does not extend to all other dangers, such as systemic poisoning from such dyes. This case was heard on our motion to dismiss, and the Toilet Goods motion for summary judgment. Neither of us won, and the court set it down for hearing on the merits of what Congress actually intended by the new law. The case was supposed to go to trial today. Instead, the Third Circuit Court decided the generic name case, so we reinstituted our motion to dismiss.*

The reports and records case was also in Wilmington, and was also brought by the Pharmaceutical Manufacturers Association and 41 of its members. The purpose of this suit is to obtain a judicial ruling that the industry is under no obligation to keep records and make reports on drugs that we have approved as new drugs in the past and which became generally recognized as safe prior to the enactment of the 1962 Amendments. The more important issue, of course, is whether we have the right to insist that these drugs be shown to be effective as well as safe and to require the industry to support their claims. This is the first skirmish as to the applicability of the 1962 amendment to previously approved drugs. This case has not been heard. We filed a motion to dismiss, and since it is before the same judge who had decided the "generic name everytime" and involves the same procedural issues, it was delayed. This case will be controlled by the Supreme Court's decision in the case that it has agreed to review.

New Drug Procedures

Mr. Depew: Is it FDA's opinion that a new drug will never become an old drug and thus be outside the new drug controls of the Kefauver-Harris Drug Amendments? How about dipyrone?

* The FDA appeal of the *Toilet Goods Association* case has since been decided by the United States Court of Appeals, Second District, which reversed in part and affirmed in part the decision of the district court. See Food Drug Cosmetic Law Reporter, ¶ 40,225.

Mr. Goodrich: We are not of the opinion that a new drug will never become an old drug. We do take the position that there is a continuing responsibility to report an experience with a drug that has been approved through the new drug procedures. And if a new hazard comes up, no matter how old the drug is, it becomes a new drug because it can no longer be generally recognized as safe.

Dipyrone came on the market in the mid-30's before the passage of the 1938 amendments. It was, therefore, under the grandfather clause of the 1938 amendments and was not a new drug so long as it was marketed for the conditions for which it was labeled in 1938. Even though it was marketed for those conditions it was considered quite dangerous. We took action against it, by removing it from the market as misbranded. It could come back with new labeling only by a clearance through the new drug procedures. The point here is that no matter how long a drug has been on the market, it is a new drug at any time when new doubts about its safety are encountered. We had a case in the Tenth Circuit Court involving another issue of grandfather clause interpretation involving a drug called Halsion, which is Vitamin A used for the treatment of acne and pimples. We proceeded against that product, proved it was misbranded with its grandfathered claims, and we are contending in court that it could only be relabeled by clearance under the new drug procedures.

Product Liability

Mr. Depew: What is the federal government's legal position in relation to product liability?

Mr. Goodrich: Thus far the courts have held that a mistaken clearance, for example, of a new drug by an agency is not subject to recovery under the Federal Tort Claims Act. However, drug promotional practices which purposely and knowingly withhold warning labeling as to the use of the drug may subject the manufacturer to liability claims. For example, the Mer 29 cases involve a claim that the firm knew and failed to warn about the dangers from using this drug. There are also some private claims involving thalidomide. But the major position we have to play here is that we're insisting that the labeling and advertising give a fair and complete story about these drugs. A failure to comply will probably result in some liability claims if someone gets hurt because of failure to warn. The legal profession, itself, seems to me to be just now catching on to the large amount of promotional materials that is issued for prescription drugs and to the sources of knowledge about these drugs. This

volume of drug information should increase with the increased requirements for promoting drugs under the Kefauver-Harris Drug Amendments, and may well become an important factor in product liability litigation.

Breaded Shrimp Concept

Mr. Depew: Does the Food and Drug Administration intend to apply the breaded shrimp concept to future proposals for standards of identity? If so, does the Food and Drug Administration propose an amendment to existing standards in keeping with the breaded shrimp philosophy? If the answer to those questions is in the affirmative will you elaborate on what is encompassed in the phrase "safe and suitable" ingredients as that phrase is used in the breaded shrimp standards.

Mr. Stephens: The answer to this question is yes. This concept assures development of standards that are satisfactory to consumers and which lend themselves to practical application by the manufacturers. We are hoping to reconsider all of the old standards where there are no requirements in general for the declaration of the great mass of optional ingredients. We believe the time is coming, since the consumer wants more and more information as to what optional ingredients are used in a particular standard. We think this concept also offers a great deal to the food manufacturer. Obviously there are limitations. For example, you cannot permit additives that the manufacturer conceivably might consider safe and suitable ingredients to be added if he's going to completely change the character of the article as understood by the purchaser. We must remember that the consumer has the right to purchase and receive the product she recognizes and expects. In Section 409 you will find more precise language as to what is expected in the way of food additives. Aside from the purity and safety aspects of this section you will note in the mandate to the Secretary of Health, Education and Welfare (HEW), he must determine from presented evidence whether or not a proposed use of a food additive will promote deception of the consumer and whether or not the proposed use will violate any of the provisions of the Food, Drug and Cosmetic Act.

Articles With Legitimate Non-Drug Uses

Mr. Depew: Where an article has a legitimate non-drug use, as well as a questionable or restricted drug use, to what extent is the manufacturer responsible for insuring that the article distributed by him is not diverted to a drug use?

Mr. Rayfield: We think the manufacturer should use prudence and should warn of dangers to actual users of the article manufactured solely for non-drug use. When a customer sends in an order for the article we feel that the manufacturer should seek positive assurance that the prospective purchaser will not use the material for drug purposes.

Program on Salmonella

Mr. Depew: The idea of Salmonella contaminating many of our foods is frightening! What is FDA doing about it?

Mr. Rayfield: Several years ago, we recognized the problem, therefore, a program on Salmonella is included in our long-range plans. In all of our new District buildings we established bacteriological laboratories. Each year since 1964 we have been increasing the number of examinations on foods. In addition the Bureau of Scientific Research (BSR) has been doing research to improve bacteriological methods for determining Salmonella. This research is being done in cooperation with the Association of Official Analytical Chemists. As a great many of you know, there is pending a proposal to amend the standards of identity for frozen and dried eggs to require pasteurization for elimination of Salmonella organisms. At the same time we propose to establish standards for some of the other egg products that have not been standardized, which will require these to be free from Salmonella organisms.

Information on Court Action

Mr. Depew: Following a citation, would FDA be willing to voluntarily notify the citee if the decision is made to go to court?

Mr. Rayfield: We should recognize that the Food and Drug Administration issues about 1,000 or more citations per year, and it requires a considerable amount of additional work to notify each citee. If a citee phones a District after the passage of an appropriate amount of time, and inquires as to whether the case has been abated or not he may get an answer. If the District does not know, this information may be obtained from Washington.

Zero Defects Programs

Mr. Depew: Can a zero defects program designed for the space-hardware industry really be translated into a program for the drug industry?

Mr. Delmore: Yes. Many people have the mistaken idea that zero defects is only applicable to firms that might produce hardware

and even other types of material. As far as I am concerned every drug should be produced under a program which does not permit errors. This is no different from the missile industry. Zero defects programs help an organization remove inherent defects in all phases of its operations. It can motivate all employees from top officials to the last employee to strive toward error-free performance. There are now some 1,500 firms involving 1,500,000 employees in this country which have zero defects programs. Recently two drug firms have adopted the program and others are interested. Surely these firms would not go into this program unless it benefited them.

FDA Seminars for Industry Groups

Mr. Depew: Under what circumstances will FDA plan seminars or workshops with an industry group with a problem?

Mr. Delmore: First, I would suggest that seminars and workshops for industry groups be industry-wide. I think you can understand my viewpoint. Second, the group should come to us with a specific problem or problems so we can contact the people in FDA to provide the answers or guidance needed to comply with the law.

Consumer Education

Mr. Depew: Is it not possible that the consumer's indifference stems from the fact that she is led by industry and government to believe that she is being protected, that her food is nutritious; not that she understands the full implications on health of an increasing percentage of fabricated foods in the diet and that she approves of this trend?

Mr. Delmore: Let me start by saying that I am not aware of "consumer indifference." If you get the kind of mail we get and the confidence we see reflected by consumer groups, I'd say that consumers are not indifferent. What appears to be consumer indifference may stem from the lack of knowledge of the complexities of today's food technology. I think this is one of our problems in standards making. The standards-making concepts are based on the premise that the housewife understands use of ingredients used in food supply, and she buys accordingly. This was true at one time, but I doubt that it is true today. Therefore one of our big jobs and that of the food industry is better product understanding by consumers so that there will be a better appreciation.

Mr. Depew: In these days, when the school curriculum is so crowded with basic subjects like science and international relations, do you think schools should teach consumer education?

Mr. Delmore: Yes, I most decidedly do. What subject can a high school student—who will be a breadwinner or a homemaker in a few years—learn that is more important than how to safeguard a youngster against poisoning, how to avoid phony cures and fake medical devices, how to think critically about labeling and advertising. If we had the time—and I had the letters with me—I could quote at length from letters we get from young householders who complain because they never learned these things in school, and need them now.

Mr. Depew: What coordination is being planned between the FDA consumer education program and the government's anti-poverty program?

Mr. Delmore: FDA consumer consultants in the field are already working with local Community Action Programs wherever such programs provide for consumer education. FDA is also adapting some of its printed material into simplified version for use with lower reading level groups. Material is also being translated into Spanish, and will be translated into other foreign languages, for use with the Cuban, Puerto Rican, and similar population segments.

Review of Existing Food Standards

Mr. Depew: Many food standards are now 20 years old or older. Does FDA have any plans to review and revise them?

Mr. Roe: Yes, we do have such plans. We realize many of the standards have been in effect for many years during which there have been technological changes; therefore, our long-range plans, discussed a short while ago, include the review of the existing standards.

Paper Cups and Plates

Mr. Depew: What is the status of paper cups (hot and cold drinks) and paper plates under the Food Additives Amendment?

Mr. Roe: I doubt that paper cups and paper plates, per se, are ordinarily products that would be subject to the law. But you will note that we have a number of regulations established under the Food Additives Amendment that deal with what we call indirect additives, that is, substances or constituents of products that are in contact with foods that might result in migration to the foods or in some way affect the food. The regulations to which I refer deal with paper, paper board containers of various kinds, and rubber belts and other materials and utensils that come in contact with foods during manufacturing and packaging operations. The purpose of the regulations

is to provide the specifications, tolerances, and definitions for the ingredient materials that are appropriate for momentary, intermittent, or extended contact with food as packages or handling equipment. I think the regulations, set up in these areas, give a pretty good guide for those manufacturers of paper plates, cups, and household utensils that want some assistance regarding specifications. These regulations were promulgated to prevent inadvertent contamination of the food by migration of substances into the food product.

Color Additives

Mr. Depew: Are there any conditions under which a product containing a natural color ingredient, as defined under the Federal Food, Drug and Cosmetic Act, must be labeled as being artificially colored?

Mr. Roe: Yes, color additives subject to listing under the Color Additives Amendments include natural as well as synthetic colors. However, in certain food standards distinction has been made between "artificial" color and "natural" colors in providing that the latter may be declared by its name, such as grape juice, instead of "artificially colored."

Safety of Vitamin D

Mr. Depew: What is the legal basis of the new policy with respect to Vitamin D?

Dr. Kline: About a year ago, the question of safety of Vitamin D was raised by the Chief of Pediatrics of John Hopkins University. We asked the advice of two expert committees who made recommendations with respect to the restriction of use of Vitamin D. This raised the question of the safety of Vitamin D, which for many years has been generally recognized as safe. Thus under terms of the food additive section of the law a proposal was made to restrict the amount of Vitamin D added to certain specified foods. There is in that proposal, as you may remember, a statement of policy which declares Vitamin D in amounts over and above that necessary for good nutrition is a drug. Now it is significant, I think, to recognize that it proposes a sharp delineation between Vitamin D as a nutrient, and Vitamin D used for therapeutic purposes.

International Drug Reporting System

Mr. Depew: Has the FDA proposal to establish the world-wide adverse drug reporting system been adopted by the World Health Organization (WHO)?

Dr. Kline: Yes, this international reporting system has been approved in principle by the WHO and the plans are in final process of being approved. The plans for the structure of the organization calls for the International Center to be located here in Washington in the Food and Drug Administration. This will be the center for collecting and reporting adverse drug reaction information, from a number of participating countries, through the WHO office. It's expected that this will be fully implemented by next July.

Dietary Food Regulations

Mr. Depew: What is the current status of the special dietary food regulations?

Dr. Kline: We are now reviewing what we hope is a final draft of the special dietary food regulations proposals. As you know, this has been some time in preparation but there have been many difficult problems to resolve. We hope that the regulations will be before the Commissioner for signature soon.

Synthetic Food Additives

Mr. Depew: It was stated that drugs which are equivalent by chemical assay may not be biologically equivalent. What implications does this have upon the increasing use of synthetic chemicals in foods?

Dr. Kline: In the review of a petition for use of a synthetic food additive we require, in addition to a feasible chemical assay of the substance, a showing that the substance, if offered for its physiological or biological properties, does in fact exert such an effect in the animal or human body. Such tests must be applied to the substance in the form in which it is to be used in the food.

Zero Penicillin Cross-Contamination

Mr. Depew: It has been stated to pharmaceutical manufacturers conferring with the Antibiotics Division and other FDA scientists that penicillin cross-contamination should be zero. This is a laudable aim and should be attained—but what is zero? Has FDA or any agency developed methods which are sufficiently accurate and sufficiently reproducible to insure that "zero" or even a working tolerance is accurate to a satisfactory applicable degree?

Mr. Kirk: The question of what is zero comes up in a great many areas. It is particularly applicable to pesticides where we have zero

tolerances. In that area, just five months ago, a report was received from a distinguished committee of the National Academy of Sciences. We and the Department of Agriculture are reviewing this report to see how we can implement the committee's recommendations in light of the present law. As the inquiry here recognizes, it is impossible to prove zero absolutely by chemical or other analysis. All we can do is to apply a method of the best sensitivity we have, which for penicillin cross-contamination happens to be .05 units. That, of course, is not zero, and there may be contamination below that level but we can't prove it by presently available methods. We want to get as close to zero as technically possible in this particular area, but I doubt that there is any immediate prospect of getting any closer.

Proceedings of Medical Advisory Committee

Mr. Depew: Are the proceedings of the Medical Advisory Committee reduced to writing and are they available to interested persons?

Mr. Kirk: The proceedings of the medical advisory committee are reduced to writing because there is a requirement that at all of these proceedings there must be a secretary to keep the minutes of the meetings. Now, when we take any action with respect to the recommendations of a committee, the committee's findings are made available at the office of the hearing clerk if they are not brief enough to publish in the Federal Register.

Pesticide Residues

Mr. Depew: What steps have been taken by FDA to implement the recommendations of the National Academy of Sciences—National Research Council (NAS-NRC) Committee on zero tolerance regarding pesticide tolerances and no residue registrations?

Mr. Kirk: Food and Drug Administration and the Agricultural Research Service of the Department of Agriculture got together a task force to go over each recommendation of the National Academy of Sciences' Committee to determine what, if anything, could be accomplished without new legislation. That task force worked very diligently and we believe that shortly we should be able to present the committee's recommendations to the Secretary of HEW and the Secretary of Agriculture. Keep in mind that they are the ones who asked for the Committee in the first place. It is pertinent that the No. 1 recommendation—"Let's get rid of zero tolerances", of course cannot be accomplished without legislation. However, in the next

paragraph of the Committee's report, there is a recommendation that very low levels be set for pesticide residues resulting from purposeful uses of pesticides and that recommendation can be accomplished under the present law where there is adequate scientific evidence of safety and practically the tolerances can be met. It is with this objective that the task force has been working.

Public Administration Service Report

Mr. Depew: What are the FDA views in general regarding the recommendations of the Public Administration Service report and what, if anything has been done to implement it?

Mr. Kirk: Basically, this report, as you probably heard this morning, involves 3 broad areas—first, federal, state, and local governments should enter into a balanced partnership with the proper role for each delineated. To arrive at this partnership we have to have more uniform, stronger, and upgraded programs all along the line. And the report recommends that the federal government, and FDA in particular, should assume basic responsibility and leadership in the development of these roles; further, that the federal government should provide for financial and technical assistance to the states to strengthen and upgrade the implementation of their laws and programs. As far as financial support is concerned, this is a matter that will have to be taken up through the Congress, because we do not now have any grant authority as have some other government agencies, such as the Public Health Services. We have, however, undertaken to implement some of the recommendations in this report through training programs with the state people. We have integrated the development of work plans by our District offices and state agencies. This has not gone as far as we would like it to, but the Districts which have been able to get into this kind of planning report that there is every hope that it will work out well.

Addition of Overages

Mr. Depew: Since there are apparently problems with the stability of drugs and antibiotics, where the bio-dosage levels are controlled is it permissible to add overages to prevent deficiencies in products several months or more old? If in the opinion of the panel the answer is no, then are there other ways—labeling or otherwise—for the product to conform to federal and/or state requirements?

Mr. Kirk: Generalities are not very useful. Potency requirements may vary depending upon the individual product. Keep in mind that the great majority, if not all, of our antibiotic monographs have provisions whereby the potency of the drug must be within specified limits, such as 85% to 115% of the represented potency, and that the lower limit is set to take care of the reasonable loss. But you are not going to be able to provide against deficiencies forever, and by the same token there may be situations where an overage would be critical and the product could not be marketed as such. As we see it, this comes down to a specific product under a specific set of circumstances. When the available evidence indicates that a drug, vitamin or other product is subject to deterioration naturally we want to see these articles bearing a proper expiration date on the label. So, if from the evidence one can conclude that the article is subject to deterioration, it seems to us that the only legal course of action from your standpoint and the public standpoint requires that you cause a realistic expiration date to be placed on the article to guide purchasers and users as to when the product is no longer useful for the purpose intended.

FDA Research Program

Mr. Depew: At the dedication of the new FDA building, we saw and heard a lot about FDA's research program. Are the results of such research public information, and if so, how can we know what is discovered?

Dr. Summerson: The results of the FDA research program are disseminated in various ways, the most common way being that used by most research organizations, and that is the publication of scientific papers in the open literature. Another way in which the results of the FDA research program become available is when they lead to the establishment of pesticide tolerances, of food standards, and similar results of this type, which form the basis for much of the research we do. Recently we have collected all of the research publications for one year of the Bureau of Scientific Research (BSR) of FDA and bound them into a single volume, entitled "Selected Publications," which is available to all interested people. (Copies may be obtained on request from Director, Bureau of Scientific Research, Food and Drug Administration, Washington, D. C. 20204).

Mr. Depew: We hear a lot about pure research, applied research, and practical research. What kind does FDA do?

Dr. Summerson: The type of research that we have in FDA, in BSR, as well as in all other elements of FDA as far as I know, is *applied research.* This is research which has a specific objective in mind, and these objectives are guided by the requirements of the Food, Drug and Cosmetic Act. We do not do research on cancer, for example, because we are interested in the causes of cancer. We do research on cancer-producing chemicals because they may come under the requirements of the Food, Drug and Cosmetic Act. So, as far as I am concerned, all of our research is applied research. If Congress wants to support basic research, it can do so through various agencies such as the National Science Foundation, the National Institutes of Health, and other government agencies. But from our point of view, the research dollar of FDA supports the research requirements of the Food, Drug and Cosmetic Act, which is applied research.

Reduction of Drug Availability Time Lag

Mr. Depew: What are the steps being taken by FDA to reduce time lag between discovery of a new drug and its availability to consumers?

Dr. Kelsey: I believe we can help a great deal with this in the Investigational Drug Branch. We try to review the notices as quickly as possible and to point out the deficiencies, particularly those that would stand in the way of getting an approved new drug application. Our concern in the Branch is mainly about safety rather than efficacy. If a sponsor wishes to discuss the adequacy of his clinical plan, with regard to efficacy, we will refer him to the Medical Evaluation or Surveillance Branches for discussion of the design of clinical studies acceptable for a new drug application. We believe that the present system has already helped and that we are now expediting the approval of new drugs.

Termination of DMSO-IND's

Mr. Depew: Why were the dimethylsulfoxide-investigational new drugs (DMSO-IND) terminated?

Dr. Kelsey: One such IND was terminated because the sponsor permitted the widespread distribution of this drug in Phase III studies without informing the Food and Drug Administration of its action. Furthermore, some of these plans were not covered in the IND; therefore, they permitted uses we felt were not supported by the preclinical data. Secondly, the remaining IND's were terminated when we learned of the defects in the eyes of several species of animals,

including dogs, rabbits, and hogs. These occurred first at dosages roughly of the same order of magnitude as would be administered to humans. We had no information whether or not this adverse effect did occur in man, but we felt the studies should be delayed until we received more information. Also, there was widespread distribution and unauthorized use of this drug.

Podiatrist's Participation in Drug Evaluation

Mr. Depew: How many specialists in podiatry participate in the clinical evaluation for safety and effectiveness of podiatric drugs?

Dr. Kelsey: Podiatrists licensed to administer drugs may participate in the clinical evaluation of the safety and effectiveness of these drugs if the sponsor of the drug feels they are qualified to do so. As with all investigations, they should meet the scientific training and experience considered appropriate by the sponsor for the proposed study of the drug.

Policy Concerning Meclizine

Mr. Depew: What is the legal basis of the new policy with respect to meclizine?

Dr. Kelsey: Meclizine is reported to produce a cleft palate and certain other congenital anomalies in several species of animals. While clinical studies that have been reviewed have failed to indicate any conclusive evidence that meclizine is harmful to the human embryo, a very large number of women receiving the drug at a critical period of pregnancy would have to be carefully evaluated in order to rule out the possibility of adverse effects in an occasional individual. Meclizine is available on an over-the-counter basis for nausea and vomiting associated with such conditions as travel sickness, and on prescription for the treatment of nausea and vomiting of early pregnancy.

In view of the lack of substantial evidence of the safety of this drug in human pregnancy, we deemed it advisable to require a description of the animal findings in the brochure of prescription preparations of the drug. Because of this, it appeared essential that a warning of the possible hazards of the drug in pregnancy should also appear on the over-the-counter preparations of this same drug.

Consideration was given to making the drug a prescription item only but this was not done in the absence of any convincing evidence that this drug was harmful in human pregnancy. **[The End]**

Toxicologic Aspects of Drug Safety

By FREDERICK COULSTON

This Article Was Presented at the Symposium on the Safety of Food and Drugs, Forming a Part of the Dedication Ceremonies for the New FDA Building on November 22, 1965. Dr. Coulston Is at Albany Medical College.

TRADITIONALLY, TOXICOLOGY IS A STUDY OF POISONS as they affect man, plants and animals. Over many periods of years, man has been exposed to chemicals of various kinds. The modern concept of toxicology applies to the multidiscipline approach to the problems of the handling of chemicals and drugs by human beings and animals. In this concept, modern toxicology is indeed a marriage of pharmacology, biochemistry and pathology. The air we breathe, the food we eat, the water we drink, the clothes we wear, the drugs we use; these *are* the concern of modern toxicology. Such episodes as the thalidomide problem, excessive radioactive fallouts, smog, water polution, pesticides, carcinogens, smoking—and, pretty soon, I suppose, even the problems of sex—are all parts that make up modern toxicology. Anything that has to do with the handling of drugs or chemicals in the body, particularly the safety evaluation of these substances, is the realm of modern toxicology. In the past, it was rather simple to study a drug or a chemical. And I should say at this point that mostly all chemicals sooner or later can be considered drugs, because in the course of events new uses are often found for even such things as arsenic or pesticides, and these rather toxic substances may become useful drugs to both animals and man.

The human race has been exposed over a period of many years, sometimes hundreds of years, to such chemicals as arsenic, lead, fluorine, copper, pyrethrum, natural flavors and even spices. The proof of safety was relatively simple, as compared with that needed for modern drugs. The proof of safety simply consisted of the ex-

perience one had in man. If man got sick from taking too much arsenic, the signs and symptoms were very readily recognizable and, in the early days, man rather than animals was the species of choice for the actual determination of toxicology. With the modern explosion of hundreds and hundreds of new synthetic chemicals which are used today as medicines, pesticides, feed and food additives, there has been introduced into man many new substances to which he has had no previous experience. Our concern must be with the whole direction of chemical product synthesis and the impact of these substances on man. Drugs are an important element of this chemical technology, but so are pesticides, food additives, and even cosmetics. What we are talking about are the products of the chemistry laboratory which, apart from their original purpose, whether it be therapy, worm-free apples, greener looking peas or redder lips, manage to find their way into man's physiology. No one can deny the importance of these chemicals to the general welfare of the human race, but we must assure man's safety as he is increasingly exposed to chemical agents. Obviously, a tremendous series of problems have been created. As civilization advances, man must use the products of this remarkable chemical explosion, but he must, in some manner, control the outcome of these advances. The problem is not simply that of a man taking a drug but also concerns the air we breathe, the water we drink and the food we eat. The need for the study of these problems is indeed the concern of our program today. Particularly, there is a great need for improved methods of predicting from animal research exactly what will happen when these chemicals, be they drugs or pesticides, are given to man for the first time.

Three Ways Man Is Exposed to Chemicals

There are usually three ways in which man is exposed to chemical agents. The *first* and most carefully controlled situation is when the physician prescribes a drug for his patient. Here, presumably, informed decisions are being made as to the properties of the drug and the peculiarities of the patient. *Next* are the over-the-counter drugs—the one-to-one relationship of doctor to the patient is now lost. Instead, the patient gets his protection in a printed warning to see his physician if his cough or pain persists. The *third* category of what amounts to drug taking is removed from the area of individual choice entirely. I refer to chemical additives used in food processing. The individual who wants additive-free foods had better tend his own garden since even the humble bread on his table may contain as

many as 30 chemical ingredients today. However, the addition of a chemical substance to food is deliberated, and is done for a reason. No one today would consider using a hard old loaf of pumpernickel containing much straw and debris as a suitable medium for making a sandwich. But man's ingestion of pesticides remaining on agricultural products is often inadvertent, and its possible consequences are not yet fully known. Between food additives and pesticide residues, we have, in effect, 190,000,000 Americans consuming non-prescription drugs every day. I mention these things purely as a reflection of the kind of chemical environment we have created.

Control of Environment

The true situation is that we enjoy unmatched nutritional abundance and a superior level of health, in very great part because of this great inventiveness in using chemistry to reshape our environment; and we have reached the point where man indeed can and perhaps must control his environment. We would find it difficult to imagine the treatment of diabetes without insulin, of pernicious anemia without Vitamin B_{12} or of adrenal deficiencies without the corticoids. Michelson has estimated that, without insecticide spraying, only nine to ten percent of certain crops could be produced. In the past 25 years, over 14,000 applications have been made to the Food and Drug Administration (FDA) for approval to market new drugs or combinations of drugs. Nine out of ten drugs in use today weren't even known prior to World War II. The tide of new pesticides and food additives has been equally impressive. Our interest today is not only with the pace of chemical synthesis but with the character of it. With sulfonamides and antibiotics, we are concerned with toxicologic effects that are symptomatic and usually reversible, but with the advent of cortisone and the steroids we are usually dealing with profound and irreversible effects. To questions of acute toxicity, we must now add a concern with chronic and cumulative reactions. The problem of one or more chemical substances working in a fashion to interfere with or augment the other is, indeed, a very important problem. We must address ourselves to what Richards has called the metabolic toxicities. We have drugs, for example, whose action blocks basic metabolic processes like cholesterol synthesis.

Back in 1900, which is aeons ago in drug history, the great Paul Ehrlich pointed to the wonders of anti-toxin and anti-bacterial substances which he called "Charmed bullets which strike only those

objects for whose destruction they have been produced." If this, indeed, were only true this afternoon, there would not be as much a problem as does exist. Too many of our chemicals today are broad-spectrum, not only in their effects upon a particular target organ or bacteria but in their wide-spread physiologic activity against certain areas of the body as a whole. We have analytical techniques available to us today that make the laboratory of yesterday seem as quaint as the alchemist's workshop. We have spectrophotometry, chromatography, radioactive tracers, tissue cultures, electrophoresis and improved methods of bioassay, and the roster of professions engaged in safeguarding drug and food supplies is lengthy and impressive. Biochemists, biometricians, pathologists, and pharmacologists do not begin to complete the list. Yet, for all this technique and talent deployed in the public interest, the public's protection is not complete. As the Commissioner of Health of the State of New York, Dr. Ingraham, recently stated:

> I can think of no sphere of economic activity where heavier burden rests on both industry and government to protect the citizen than the area of chemical agents which effect man.

This is particularly true because public trust increases in direct proportion to the complexity of a situation.

Role Played by FDA in Beginning of Modern Toxicology

Modern toxicology begins about ten years ago. Most toxicologic research at this time was done, and, I might add, is still being done, in the laboratories of pharmaceutical companies and certain heavy-chemical companies. This research was done because it was important for the various companies to know how safe and effective their products were. I think it is apparent that all good companies who have been successful over the years are indeed concerned with the product that they put before the public; yet we must recognize that the Federal Food and Drug Administration (FDA) has played an outstanding and leading role in this program. The universities and medical centers were concerned in their research programs more with efficacy than with safety. The various departments of pharmacology throughout the country, if not the world, were also more concerned with the problems of efficacy and the mechanisms of actions of drugs in particular. The necessary research for the understanding of the safety of compounds was indeed held in limbo. Except for LD_{50} determinations, most centers of pharmacologic research did not spend much of their effort on the problems so necessary for a correct evaluation

of the inherent toxicology of various chemicals. Who, indeed, wanted to spend the rest of their lives counting the dead ones that appeared after the administration of a particular drug? Who, indeed, wanted to spend his time medicating rats for two years or dogs for perhaps five to seven years? This type of research was not very attractive and often did not bring the good scientists into the field of toxicology. Toxicology, as it existed at this time, was primarily the concern of the industrial toxicologists and the people involved in forensic medicine. How much of a particular noxious substance had to be in the atmosphere of a chemical plant before the workers became ill? How much barbiturate was present in the stomach contents of a particular subject who died in a suicide attempt or as a result of a criminal act?

Revolution in Toxicology

Without spending too much time in reviewing the revolution that has occurred in toxicology, it is important to mention a few salient episodes. The creation of a Gordon Research Conference on Toxicology and Safety Evaluation, with Dr. Ben Oser as first chairman, was an important step forward. For the first time, people interested in drug toxicology met with those already established scientists interested primarily in industrial toxicology and hygiene. This, in itself, I can attest, created much friction at first, but resulted in a better understanding of the problems of each of these groups. It provided, for a first time, a public forum where methodology as well as information could be disseminated and discussed by a scientific body of dedicated professional research men. As a result of many discussions held at this Conference, there was founded, by Dr. Arnold Lehman and myself, a new journal called "Toxicology and Applied Pharmacology." The purpose of this new journal was to provide a central place for the publication of not only positive data but much of the negative data so necessary in the establishment of the safety of a particular chemical. Under the leadership of Dr. Harry Hayes, and, soon afterwards, Dr. Kenneth DuBois, this journal has established itself as one of the important areas for publication in the field of toxicology. This event was soon followed by the creation of an International Society of Toxicology which has now approximately 350 members. The great need for research and training in toxicology that exists today has been recognized by such eminent scientists and administrators as Dr. James Shannon, Director of the National Institutes of Health. At a meeting three years ago of the Gordon Research Conference on Toxicology and Safety Evaluations, he pointed

out that there was a great need in toxicology for the development of programs in depth, to get at the basic mechanisms of how drugs interfere with or augment various body processes. He called at that time for the creation of centers for research and for the training of toxicologists dedicated to working on the principles of toxicology. At the recent fall meeting of the Pharmacology Society, he again affirmed his belief in this approach and pointed out that it was necessary for the various centers of pharmacology to recognize this great need and to set about doing research so greatly needed for a better understanding of how chemicals and drugs may interfere with everyday exposure in our total environment. Today, through the leadership of Dr. Shannon, several national centers for toxicology have been created and it is the hope of all of us that important research will come from these new centers. It was his belief that most pharmacologists in this country have not been realistic and have not adopted a sense of public responsibility with respects to the problems of chemical intoxication. The magnitude of the effort on the part of pharmacologists to seek solutions to such problems has failed almost entirely to keep pace with the rate at which they (the problems) have been created as a result of the introduction of a wide variety of chemicals into our environment. Dr. Shannon shares with many of us his concern about the need to interest bright young scientists in studying toxicity in depth, and about the lack of knowledge and scientific interest in insecticides and food additives, particularly with respect to long-term exposure.

Report of the President's Science Advisory Committee

Recently, the President's Science Advisory Committee presented a report which, in essence, sums up much of the previous thinking of many scientists. In this report, the primary concern was with pesticides, but the general statements are applicable to any drug or chemical. The report emphasizes the need to know more about the effects of various chemicals on fertility, size and weight of off-spring, fetal mortality, teratogenicity and the growth and development of the newborn and the juvenile. The nature of the chemicals and drugs such as tranquilizers, steroids, hormones, analgesics, et cetera, must be considered also. The Advisory Committee pointed out that there have been very few systematic studies designed to learn how to predict the consequences in man of the use of a given drug or combination of drugs. These problems were emphasized by the recent report of the National Academy of Science's Sub-Committee on "The Use

of Human Subjects In Safety Evaluation of Food Additions and Pesticides." Yet, the role of the Food and Drug Administration over the years in doing research of its own on these many problems and of stimulating very important and necessary research, both in industry and wherever possible in academic life, must not be overlooked. The FDA's need to know how chemicals behave in both man and animals is directly related to its role as a regulatory agency in the protection of the national welfare as pertains to foods and drugs. It has, over the years, generated data, both in-house and outside, that is necessary for the carrying out of its mission. In this way, it has advanced the general knowledge of toxicology and in many ways, the mechanisms of efficacy, as well.

Modern Safety Evaluation of Drugs and Chemicals

The modern safety evaluation of drugs and chemicals utilizes the principles of pharmacology, biochemistry and pathology to such an extent that it is often difficult to categorize the discipline involved. By the use of the modern methods in these scientific areas, a new comparative understanding of the cellular changes induced by chemicals must be sought in experiments involving the embryo, the newborn, the juvenile and the adult of various animals, particularly the rhesus monkey and man. In general, information concerning the metabolic fates of various drugs and pesticides in man is not correlated with animal data. A logical prediction of toxicity in man must depend upon a proper choice of the correct animal species in terms of the metabolic fate of the chemical.

A major aim of modern toxicology is to determine the possible basis for such logical predictions. The use of new and old drugs and chemicals, as therapeutic agents, pesticides and food additives, has created many problems relating to the safety of the individual and the community. The criterion of safety is the toleration by man of multiple administered doses. Only by a multidisciplinary scientific approach can these problems be understood. The need to know from animal experimentation what species and what combination of measurable parameters may be useful for a logical prediction of the toxicity of an unknown compound in man is most urgent. Obviously, all the possible parameters cannot be studied for every new drug, and it appears desirable to study in great depth those drugs or chemicals to which man has had undesirable reactions, or where there is

question about his exposure. By going back to the animal models, in depth and with modern instrumentation and techniques, some parameters may be discovered which either were missed or were not apparent with old and classic techniques. These studies should give a greater insight into the early changes found at the subcellular level during a relatively short chemical exposure time, and should permit comparison of these changes with those produced by chronic or repeated exposure. The specific aim of such a program should be to correlate morphologic alterations manifested by light microscopy, histochemistry and electron microscopy with precise biochemical changes in tissues following the administration of various pesticides and drugs. The relationship of physiologic and pathologic changes in both acute and chronic experiments must be demonstrated. Whether the problem deals with food additives in studies on atherosclerosis, or the effects of a drug on the hepatic cells, basic principles of pathology must be employed and used with those of pharmacology and biochemistry.

Ways Drugs Affect Body Cells

Modern toxicologists have come to learn that drugs are handled in peculiar ways by the body: "peculiar" in the sense that each drug —each class of chemicals, in other words—has a characteristic that can be recognized in the cell. We have, indeed, come to the age of molecular toxicology and pharmacology, because we are now studying at a subcellular level the events that occur when a new drug is given to man. Obviously, certain biotransformations can occur. If the chemicals are rapidly metabolized, then the therapeutic level cannot be reached because the drugs are excreted too rapidly. On the other hand, if the drug is excreted very slowly or not excreted at all, it accumulates in the body, and then we say that the drug can become very toxic. But in all these events, there is a physiologic adaptation that occurs which can often be visualized by the use of the electron microscope. These changes may be related to the mitochondria, or to the endoplasmic reticulum, or to other internal organelles of the cell. The drugs may be in competition with each other or with certain body chemicals, as bilirubin for the same binding sites on a protein. Many liposoluble chemicals can induce microsomal enzymes and, by virtue of this induction, these drugs metabolizing enzymes carry out reactions such as oxidation, reduction or hydrolysis at an increased rate.

Whether these chemicals are drugs, pesticides or food additives, they are consequently excreted in various forms and may be excreted as the parent compound, or in various different chemical configurations. Phenylbutazone, for example, may enhance its own metabolism, as well as that of many other drugs. The problems become very complex. Is the activity of a drug due to the parent compound or to a metabolite of the drug? Different animal species may metabolize the drug at different rates. The effect of various enzyme systems, such as the drug metabolizing enzymes, may more actively metabolize a particular drug than would ordinarily be expected. There may be differences, in protein-binding and, last but not least, the drug may, in essence, act as an irreversible protein coagulant and block most of the metabolic systems.

Choice of Species for Toxicologic Studies

The choice of animal species for toxicologic studies, therefore, becomes a very important subject. We cannot, for example, decide easily which animal should be the species of choice. For example, mice can deaminate many chemicals; rats cannot. Dogs usually do not acetylate drugs; monkeys can. Unfortunately, this is simplifying the situation too much, since, with a drug such as isoniazid, some men act like monkeys, while other men act like dogs, in handling the drug. The ideal would be to have a drug with a half-life, that is, a plasma level, that allows the chemical to stay in the blood and tissues for at least a time necessary to do its therapeutic or chemotherapeutic job. It is very desirable, therefore, to find out as early as possible how a drug is handled by man in the metabolic sense, and then go back to the animal so that the proper species can be chosen for toxicity studies. Certainly, in time we will have cataloged the major classes of drugs and the way in which various animal species handle these drugs metabolically so that this type of research will not be necessary. At present, it certainly seems to be.

Extrapolation of Animal Data to Man

The legitimate question can still be asked, since we do not have the answer: How can we be sure that the extrapolation of animal data to man is accurate? Complicating the picture is the fact that often in man we study the toxicology of a compound in a sick person. Unfortunately, this is extremely difficult to do in animal research, because we have not reached the stage where models of human dis-

ease can readily be obtained in animals. Consequently, pathologic states may change the toxicity, and, indeed, the efficacy of many drugs.

Extent of Toxicity Studies

The trend in modern toxicology appears to be a reversal of the common practices. Because of our general ignorance about how chemicals are handled by various species of animals, we have required longer and longer periods of medication as a safety precaution. In 1940 it was not uncommon to call a study of 30 days of medication a chronic toxicity study. It was only necessary to study a few rats, a few rabbits and, possibly, a few mice, but as the sophistication and the lack of correlation developed between animal and man, we began to add more and more studies, more and more species, lengthening the extent of the studies until finally we were at the point where it is not uncommon to do life-time studies in the rat and, indeed, five year studies in the dogs or their equivalent, the monkey. At present, I don't know of any other way to do it than just that way. However, our hope is that we can learn from a few animals given large amounts of drugs over a very short period of time all that we need to know about how a particular drug enters physiologic systems of the body.

Prediction of Systemic Changes

With many drugs, it is relatively simple to say that a drug is safe if it affects a particular organ system. We do not have much difficulty in describing changes in liver, for example, with a drug. We can predict usually, from animal studies, that this will also occur in man. The areas where it becomes, at the present time, almost impossible to predict from animal studies what will occur in man is in the general category of what we call allergy, idiosyncrasy, or hypersensitivity in general. In brief, then, the aim of modern toxicologists is to discover defects in animals at very high doses, find the target organ or system, and then see if these changes can be observed in man at very low doses. To say this another way, we attempt to use high or unreasonable doses in animals and then carry the information to the first studies in man with reasonable doses; that is, doses that will not hurt the person. These reasonable doses may be within the range of the effective doses for a particular disease condition.

When a drug is studied in this way, it may be that a three to six month animal experiment is all that is necessary, provided cellular models

are included. For example, changes can be observed as early as 30 minutes at a subcellular level with many chemicals that we know of today. Indeed, the use of the intact unanesthetized animal to gain continuous physiologic and chemical information following the administration of large doses provides the modern toxicologist with a wealth of instantaneous data. If it can be proven that these changes are indeed the manner in which the physiologic adaptation of this particular chemical occurs, then this would be sufficient and should supersede chronic toxicity studies of longer than six months.

It is becoming more and more apparent that until our knowledge of the manner in which drugs are handled by animals as related to man is more advanced, human experience should take priority over any animal data. For example, a substance that had been used for years by man and considered safe is now put into an animal model of, say, a mouse, and a cancer occurs specific only to mice . . . What should we do? At present, the tendency appears to be to take this particular product or drug or chemical off of the market. However, this does not necessarily follow. I personally would far rather trust long-term human experience than the fact that a particular strain of a particular kind of mouse developed a tumor after X number of months of medication at extremely high doses. I think it fair to assume that all chemicals that get to man, either advertently or inadvertently, SHOULD BE STUDIED AS IF THEY WERE DRUGS! The assessment of carcinogenic risks is not necessary for most drugs, particularly in areas where a class of drugs has been studied extensively, or, in fact, has been used in man for many years without any increase in cancer.

Purpose of Early Toxicologic Trials in Man

The first clinical toxicologic trials in man should be done as early as possible. They should be done even before long-term chronic animal studies are initiated. The main purpose of going to man so early is to establish the metabolic fate of the drug and the organ-site of action as early as possible, and to correlate this information from man with animal data. If an animal handles the drug like man, then that particular species of animal should be used for the long-term chronic studies. This can be done with very small doses of drug in man, after all necessary precautions have been taken as emphasized by the Kefauver-Harris Amendment to the Food and Drug Act.

Detailed Study of Toxic Effects in Man

The possibility of a combination of toxic effects between two or more drugs must be studied in more detail. This includes the study of food and feed additives as well as natural products. It may very well be that certain pesticides stored in the fat of many people in this room may be beneficial to our general physiologic state rather than harmful. We stress, too often, the fact that all of these residues may be harmful; but recent information in a series of experiments in my laboratory indicate that this may not always be true. All new drugs, or chemicals in general, that are released for sale and use by the public should be monitored for a period of two or three years. The feedback of adverse reactions should be considered a part of any study relative to the safety of a particular chemical. We are not saying that all chemicals, be they drugs or food additives inadvertent or advertent, should be studied in man but, certainly, all those chemicals that have a risk in man based on their known metabolism and specific protein binding, should be studied.

An ancient saying goes, "There is no life without risk—risk is our companion from birth to the grave." Both the inevitability of risk, and the need to minimize it, impose special responsibilities on all of us as our technology skirts ever closer to the chemical secrets of life. To quote Commissioner Ingraham:

> To those whose industry and genius produce the chemical agents, the manufacturers of drugs, additives and pesticides, I say your duty is to regard the human community as your own family in weighing the risks and values of your products.

I say our duty is to justify the citizens faith that someone, somewhere in this bewildering advance of science, is protecting him from unwarranted risks. All of us must be constructive but insistent voices for safer chemical technology. I agree with Edmund Burke, who said:

> The clamor of the fire bell at midnight may disturb our sleep, but it keeps you from being burnt in your bed.

[The End]

Clinical Evaluation of Drug Safety

By JOHN LITCHFIELD

This Article Was Presented at the Symposium on the Safety of Food and Drugs, Washington, D. C., on November 22, 1965. Dr. Litchfield Is with Lederle Laboratories.

MY ASSIGNMENT IS TO CONSIDER THE CLINICAL EVALUATION OF THE SAFETY of a new drug. Efficacy is included within the scope of the term safety because an ineffective drug is unsafe. I am a laboratory rather than a clinical investigator. Nevertheless, I do have ideas on my assigned topic and I want to point out that these represent my own point of view.

It is very easy to distinguish between studies in laboratory animals and those in man. It is impossible, however, to separate the evaluation of the safety of a drug in animals from that in man because the two are inextricably entwined. Also, when we consider laboratory-animal evaluation of drug safety, we must accept the reality that certain of the effects disclosed will be peculiar to the animal species studied, while others will be generally applicable to all species including man. Furthermore, we must accept the unpleasant possibility that certain effects of a drug will be discovered only when it is studied in man, and that some of these effects may be most disconcerting.

Important Questions About Clinical Trials

In actual practice, the transition from laboratory-animal studies to trials in man is a slow step-by-step procedure. Each step has as many safeguards built into it as is feasible. Because the initial trial in man represents to a considerable extent a probing into the unknown, many questions need to be posed as the study progresses.

Probably the most important question is, "What is the justification for clinical trial of this new drug?" Clinical investigators will not answer this question uniformly by any means. In fact, answers will range widely. One extreme is illustrated by asking a mountain climber why he climbed a mountain and getting the reply "because

it was there". The other will represent an extremely detailed evaluation of all laboratory-animal studies before deciding whether or not to study the drug in man. Both extremes can be shown to have been either rewarding or wasteful.

However, if the word "justification" is admitted to consideration, then a second question promptly emerges: "Is the information on efficacy in the laboratory animals convincing?" Again, different investigators vary widely in what they consider "convincing." But at this stage we have made some logical progress in that an important question is being considered. Why is this important? The answer, to my mind, is very straightforward. To put a new, unknown drug into man involves some element of risk which, of course, will be minimized. We cannot, however, justify risk unless there is a potential benefit. The benefit need not be to the immediate subject but may be one which will aid others not the subject of the initial tests. However, the risk should not be taken without being able to recognize the potential benefit.

The next question has inevitably emerged from these considerations: "Can a trial be done with minimal risks?" To answer this adequately means that all laboratory data must be considered, evaluated and weighed in terms of potential benefit against risk. How is the busy clinical investigator going to accomplish this in the face of other important demands on his time? In practice, he must depend on a digest of the information available. This digest can be supplemented as fully as he may desire, thus enabling him to develop a feeling for the validity of the information in the digest. From experience, the clinical investigator learns when, where, and how to probe more deeply.

Let me cite an example of this. An extremely able clinical investigator became aware of a claim that a particular derivative of a known antibiotic was less toxic than the parent. Wishing to probe more deeply, he wrote to me asking if we had independent verification of the claim. I was able to reply that we had studied the derivative in question. Our work showed that it was unstable and that it therefore was not only less toxic but also less effective.

Design of Clinical Trials

If the investigator is satisfied that the trial of a new drug is justified, the next big question has to do with the design of the trial.

Since every trial tends to be unique in certain respects, each must be designed to give a particular kind of answer.

The very first one may be designed to determine whether the new drug is absorbed, distributed, metabolized and excreted as it was in laboratory animals. This trial may be made at a dosage level far below the probable therapeutic dose. In the next trial the dosage may be increased gradually to a level at which drug effects can be observed. Efficacy of the drug at this stage may be completely ignored in order to establish the relation between the data obtained in laboratory animals and man.

If no insurmountable obstacle develops, there will follow a series of trials designed specifically to determine whether or not the new drug has useful effects in man at tolerated dosage levels. As these trials develop, information on efficacy builds up and approaches a point where it must be decided whether or not the drug at tolerable doses has useful actions. If the answer is no, the trials stop; if yes, they continue and expand. If the answer is yes, a second question must be answered: "Is it safe to continue the trials?"

Generally speaking, such a logical development is almost impossible to achieve. There are always conflicts of one kind or another which make the development of a new drug follow a much more irregular pattern even though the general tendency is along the lines indicated. One of the most difficult aspects of new drug development is that one must weigh risk against benefit even though both may be largely unknown, and neither can be measured numerically until far into the future.

What must be constantly kept in mind is that any attempt to be completely logical and presumably safe can lead to rejecting a useful substance. We must accept the individualists who believe that studies in humans are of great, and those in laboratory animals of little value. These experimentalists would discover the usefulness of aspirin as an analgesic and the value of digitalis for decompensated heart disease. The conformists might reject these drugs through inability to show effectiveness of aspirin in the laboratory or, in the case of digitalis, through finding its ability to cause heart block in experimental animals. There must always be kept open the possibility of important discoveries between these extreme points of view toward investigational studies.

Development of a New Drug

Against this background, let us consider more carefully the more probable course of development of a new drug. The laboratory experiments, which are concerned with the primary activity of the drug, are represented by a series of reports. These document in detail the kinds of experiments that have been done in laboratory animals to demonstrate the particular activity of the new drug which is considered to be of value. These usually include comparisons to existing substances having similar activities. In rare situations, there is no comparable substance; that is, the action of the new drug is unique. Ordinarily, there is also some preliminary information about the toxicity of the drug.

In any case, the responsible scientist must carefully review these data and look at the information as a whole. At this point, one must remember that this body of information had been growing in a more or less orderly manner over an extended period, commonly two to three years. During that period many alternatives had to be considered, all bearing on whether the best chemical substance was at hand. Consequently, there would exist reports on a variety of probing experiments that explore the strengths and weaknesses of the new drug in a variety of laboratory situations, some of which can now be seen to be highly irrelevant. All of this information must now be considered, weighed, and sorted out. It then becomes possible to prepare an overall summary directed toward clinical evaluation. This may reveal that one or more key elements are missing and, if so, additional experiments will need to be done. The summary is the first justification for proposing a trial of the new drug in man, and it is designed, in a sense, to lead the reader through the maze of detailed reports of the laboratory studies.

If the evidence and the summary are convincing, the laboratory scientist and his counterpart in medical research will sketch out the probable fashion in which the new drug will be studied in the clinic. At this stage, it must be decided that the use of the drug will be short term—that is, a few days—or long term, a month or more. The probable method of administration must also be determined. When these and other factors have been considered, a protocol for toxicity studies in laboratory animals is drawn up. This protocol is designed specifically for the drug and its intended use.

Next, the kinds of animals to be studied have to be decided and all of the available information must be considered. Frequently, at

this stage some studies in animals have been made to determine what happens to the drug in the body and, therefore, analytical methods have been developed. It may be highly desirable, if some animal toxicity data are available, to plan on the administration of very small single doses to healthy humans in order to study absorption, excretion, and metabolism of the drug. For example, even if only partial information is available regarding the metabolic fate of the new drug in the rat and dog, it would be highly desirable to find out in a preliminary way how man disposes of the drug, and a comparison of results could aid in the selection of the kind of animals to be used in the more complete laboratory toxicity studies.

Once the general protocol of the toxicity study has been settled, the laboratory scientist responsible for the study fills in the details in terms of kinds of clinical chemical tests to be made, frequency and extent of physical examination of the animals, numbers of animals, method of dosing, and so forth.

From the clinical standpoint, the summarized data at hand with certain additions form the basis for the Investigational New Drug Application. This will be filed and the initial very limited clinical experiments will be undertaken. In many cases these involve assays of one kind or another which often can only be performed by the scientists who developed the analytical methods required. Thus laboratory scientists may become an intimate part of the early clinical experiments.

It is obvious that if a drug is converted in the human body to other substances, one must be concerned about the toxicity of these other substances. With few exceptions, the metabolic products of a drug are less harmful than the parent. As many have noted, it would be advantageous to use those animals in toxicity studies which metabolize the drug as man does. This creates a problem in terms of which comes first: the hen or the egg? The development of a new drug is basically a sequential process, and there is always the problem of how sequential the process must be. If certain stages could not proceed simultaneously, the time interval from discovery to utilization would become enormously expanded. In consequence, the totally sequential process is rejected and, in the interests of saving time, non-sequential procedures are followed when possible. This applies both at the laboratory and clinical level. One consideration, however, applies overall and is a governing factor. If significant risk to the patient would be involved, only sequential procedures may be followed.

Conclusion of Laboratory Toxicity Studies

In the normal course of events, the laboratory toxicity studies are completed. Generally, the studies in animals during the first three to six months period disclose essentially all the useful information. From the medical point of view, this information is an alerting service. It leads to several courses of action. If the laboratory studies indicate that the new drug has an adverse effect on a particular organ or tissue, then special clinical studies must be made to find out if this observation applies to man and, if so, to what extent. If the laboratory data indicate that certain physical signs may be expected to occur in man, if a patient is either overdosed or unusually sensitive, then steps will be taken to see that appropriate observations are made. If the laboratory data indicate that certain clinical chemistry tests are appropriate, these would then be provided. Over and above this, the clinical investigator will be especially alert because he is treading unknown ground.

It is important to call attention to the fact that there are no shortcuts in the development of a new drug. In every case, each forward step taken has a safeguard behind it; a forward step without this safeguard is perilous. Time can be saved sometimes in the overall process by deciding that concurrent projects will be useful. The only risk involved is the expenditure of effort, which is costly. If, at a later checkpoint, the new drug is a failure, this effort was wasted if it was not essential until a later point in time.

At every step in the clinical development of a new drug there is the need to judge again and again the benefit against the risk. This is always extremely difficult because one never has all the knowledge he wants. As the clinical studies progress, more and more information becomes available but, unfortunately, the confusion rate, for a period of time, increases proportionately. This is because certain physical signs noted in laboratory animals fail to occur in man, and also certain physical signs unique to man are observed with the new drug.

Correlating Data from Man and from Animals

As the process of studying the new drug in man for both safety and efficacy progresses, the planned studies in animals draw to a conclusion and all of the information that they can yield is available. However, by this time, the clinical studies are well along ordinarily. and are yielding an ever increasing volume of data on the effects of the new drug in man. If these data are organized on a continuing

basis, their value begins to exceed by far the data from laboratory animal studies. After all, what animal can possibly yield observations which for meaningfulness approach the value of data obtained in man himself?

When studies in man are far advanced, it is safe to say that about the only relevance left between correlations of observations in man with those in laboratory animals has to do with a better understanding of which physical signs in animals were high in predictive value for man and which were not. By continually monitoring this with many drugs, we will in the future be able to indicate those physical signs that are really important and those of comparatively little value. For example, in every laboratory-animal-toxicity study a considerable effort goes into weighing each animal at frequent intervals, tabulating these values and plotting them in order to obtain a growth curve. The objective of a well-designed study is to obtain a depression of body weight gain at the higher dosage levels, while at lower levels the weight gain will be like the control. No one can quarrel with the fact that this laborious procedure by and large indicates that a toxic dose level has been found when weight gain has been depressed as compared with control. However, in man, will the drug be studied to find the level where it impairs weight gain? Obviously not! Far more important is the matter of what signs of toxicity could be found at toxic dose levels in animals. This information is what guides the clinical investigator who must look not only for these signs but also for others which could not be predicted. This is the process by which we seek to maximize benefit and minimize risk to the patient.

Use of Computers for Organization of Data

To digress for a moment, I would like to enlarge on the matter of keeping data organized on an ongoing basis. This might be a fancy way of saying "We'll put the data into the computer". Many of us are trying to do this and learning a few hard facts of life. One is illustrated by the word GIGO which stands for garbage in, garbage out. Computers cannot improve data. A second hard lesson is that computers have no built-in system for handling synonomous terms. In consequence, unless clinical records are converted to a standard vocabulary before being entered into the system, no very useful output can be obtained. To realize the magnitude of this problem one needs only to consult a medical dictionary where often from 3 to 30 synonyms can be found for a given term. The situation may be

summed up by saying that we have great hopes of some day deriving much help from computers in the process of handling medical information. Up to now, the computer has not mastered us, but neither have we mastered the computer. One can develop a great sense of frustration in this matter, in part because the computer will not perform certain things which seem so obvious to the non-computer oriented person. For example, why should it make a difference whether a patient is bleeding or hemorrhaging? Of course, if the computer is told that these are equivalent terms, there is no problem; but this illustrates a basic difficulty. The people who can program the computer to recognize that bleeding is equivalent to hemorrhaging, or that jaundice and icterus are synonomous, are most unlikely to know these facts.

Suppose we assume that, in a given situation, standard vocabulary has been used, a large amount of clinical data from a study has been punched onto cards, fed to the computer and stored on magnetic tape. At last we can ask that the data be tabulated by the computer so that we can find out what this study really showed. The results are likely to be surprising.

First, the kinds of tables must be specified by the clinicians and one obvious breakdown concerns sex of the patients. Here it may be necessary to specify quite carefully what we mean by sex to avoid misunderstanding. We next discover that some of the subjects were neither males nor females. This requires special investigation not involving a computer. Next, pregnancy is very important, especially because of the great emphasis on possible teratogenic effects of drugs. Assuming no programming complications, we learn that in our study we had a few cases of pregnancy in males. This is more interesting in certain respects than pregnancy in the female. It usually takes only a few weeks to locate the records and verify that mistakes had been made either in punching the cards or in the clinical record itself, but in some cases there is the need to locate the patient to be able to establish the facts.

Allergic reactions are important because these cannot be predicted from studies in animals. Of course, *deaths after allergic reactions* are of *great* importance to our new drug. Naturally, we want a table dealing with these observations and at that point the unsettling discovery is made that our coding system was a bit sloppy and permitted a patient to be coded as either allergic or dead. Unfortunately, the computer can't tell which is which. Correcting this again only re-

quires locating and working back to the original records and perhaps corresponding with the clinical investigator and the patient.

This may sound ridiculous, but it has happened. The incredible gap between a programmer and a clinician is almost impossible to bridge because they have no common language. The clinician cannot judge that his study is being encoded irrationally and the programmer cannot understand what it is the clinician is asking for. Without doubt, however, this communication problem will be solved as programmers become more medically oriented and clinicians develop more understanding of computers.

Risk in Drugs

Finally, in conclusion, I would like to put the matter of risk in a better perspective. First of all, there is no such thing as no risk. Every drug, every device, every procedure, every act we take involves a risk. Generally, we try to keep these risks low but we do accept, not happily of course, a degree of risk. For example, most of us drive cars in spite of the fact that annually 43,600 people are killed and 1,600,000 are injured in automobile accidents. Even of those who were not driving or even riding in a car, 47,000 were killed and 8,500,000 were injured last year. It is estimated that in an average year, 400 unborn babies are killed in automobile accidents along with their mothers to have been. Even food is not without risk! Each year many people die and many more are very ill from food poisoning. Is it safe to be at home? The incidence of home accidents is astounding—29,000 killed and 4,400,000 injured each year. I do not wish to belabor this issue but only want to conclude that drugs today offer a high probability of benefit with a low probability of harm. This is no accident; we have learned from lessons of the past and we can look forward to a better situation in the future. **[The End]**

Now ready . . .

COMPUTERS AND THE LAW

AN INTRODUCTORY HANDBOOK

Prepared by the Special Committee on Electronic Data Retrieval
American Bar Association

Robert P. Bigelow, Editor; Roy N. Freed, Stephen E. Furth & John M. Gradwohl, Associate Editors, Bernard S. Meyer, Editorial Advisor

Lawyers! Your clients are caught up in the whirlwind world of automation and so are you!

Computers have taken over! They've become a vital part of nearly every business transaction . . . banks use them, so do insurance companies. They're vital to our space program, they check out our tax returns.

Computers are used in legal practice, too: statutory research, case law searching, predicting judicial decisions—the list goes on and on. Computers affect patent and copyright law, banking law . . . even administrative law. And last, but not least, computers are now being used within law firms themselves.

Let's face it. The lawyer who isn't familiar with computers these days may very well be left in the lurch tomorrow!

That's why, back in 1961, the American Bar Association saw the need for the Special Committee on Electronic Data Retrieval. The results of the Committee's years of study and research are now in book form . . . the practical, new COMPUTERS AND THE LAW. *It tells you in quick, easy-reading style how to get along in the age of automation—paves the way for a better understanding of the mysterious language of computer technology.*

Order Now for Immediate Delivery

Computers and the Law is now ready, so use the handy order card to order your first-press copy. This is one handbook you shouldn't be without—you'll use it time and time again!

CONTENTS

Only $5 a Copy

CCH PRODUCTS COMPANY

A DIVISION OF

COMMERCE CLEARING HOUSE, INC.

4025 W. PETERSON AVE., CHICAGO, ILLINOIS 60646

FOOD DRUG COSMETIC
LAW JOURNAL

PUBLISHED BY
COMMERCE CLEARING HOUSE, INC.
PUBLISHERS of TOPICAL LAW REPORTS
4025 W. PETERSON AVE., CHICAGO, ILL. 60646
RETURN REQUESTED

SECOND CLASS POSTAGE PAID
AT CHICAGO, ILLINOIS AND
AT ADDITIONAL MAILING OFFICES

A COMMERCE CLEARING HOUSE PUBLICATION